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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,319	02/01/2002	Brian D. Ross	11203-007001/ 2207	9799

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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,319	ROSS ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *65,66,68-71,73 and 75-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *65,66,68-71,73 and 75-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

SDD

DETAILED ACTION

Claims 65-66, 68-71, 73, 75-96 are currently pending and are present for examination.

Applicants' amendments and arguments filed on 7-5-05, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

Claim 73 is objected to because of the following informalities: Applicant indicates that claim 73 as "currently amended". However, there is no specific amendment made in the claim or even if was made has not been indicated as required under 37 CFR 1.121. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 65-66, 68-71, 73, 75, 81-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sean Munro et al. (Trends in Cell Biol.1998, Vol. 8:12-15, cited in the IDS), Komoriya et al. (WO 98/37226, 8-27-98 cited in the previous Office action), and Tang et al. (JBC, 1992, Vol. 267(14):10122-10126 cited in the previous Office action). Claims 65-66, 68-71, 73, 75, 81-96 are drawn to composition comprising a polynucleotide encoding a fusion

protein comprising retention signal peptide such as Golgi membrane retention signal peptide linked to a recognition site comprising the protease cleavage sequence which is in turn linked to a reporter molecule, wherein the retention signal comprises KDEL motif or the NEFA motif or from a Golgi glycosyltransferases or is an endoplasmic reticulum retention signal and wherein the reporter molecule is either an enzyme such as alkaline phosphatase or a fluorophore such as green fluorescent protein or a fluorophore molecule and wherein the chimeric nucleic acid is operably linked to a promoter such as constitutive or inducible promoter, wherein the chimeric nucleic acid is in an expression vector, expression cassette used to transform a host cell such as a Yeast cell or is available as a composition in a Kit.

Thus it appears that the applicant has developed a nucleic acid sequence that can encode a chimeric polypeptide comprising all the above subsequences and wherein a specific protease localized in the Golgi can cleave the above polypeptide while the polypeptide is directed to or traversing Golgi.

Sean Munro et al. teaches specific roles played by the Golgi apparatus. The reference teaches that Golgi apparatus includes a huge diversity of enzymes such as those needed for glycosylation, for lipid synthesis as well as various proteases which specifically cleave specific proteins during processing. The reference also teaches that a second class of Golgi membrane proteins for which a localization determinant has been identified includes the proteases of the *trans* Golgi network. Thus the reference specifically teaches that proteins undergo not only glycosylation or palmitoylation etc. but also proteolytic processing during their passage through Golgi and that Golgi indeed has several types of proteases in house. However, the reference is silent regarding the use of any chimeric proteins for identifying such Golgi proteases.

Komoriya et al. teach a polynucleotide encoding a fusion protein comprising the cleavage site of a protease and fluorophore as a reporter molecule for use in assaying different types of proteases. While the reference teaches polynucleotides encoding fusion protein comprising fluorophores and a protease cleavage site for detecting the activity of said protease, it does not teach the targeting of such chimeric polynucleotide encoding a fusion protein to Golgi using a Golgi retention signal as part of the chimeric polypeptide.

The art is rich in teachings of using the N-terminal sequences of glycosyltransferase such as β-1,4-galactosyltransferase, or the transmembrane domain of N-glucosaminyltransferase I as Golgi retention signal and making chimeric polypeptides using the same as evidenced by the reference of Tang et al. The above reference teaches chimeric molecules comprising the Golgi retention sequence and reporter molecules such as peptidase enzyme and transferin for targeting such chimeric polypeptides to Golgi processing.

Combining the teachings of the above references, it would have been obvious to those skilled in the art, specifically those interested in identifying protease activity in Golgi, to use the sequences taught by Tang et al. and link it to chimeric molecules taught by Komoriya et al. such that said polypeptides comprise the Golgi retention signal linked to protease cleavage sequence and a fluorophore or a reporter molecule such as phosphatase and such that said chimeric polypeptides could be used to detect and identify the presence of protease specific to Golgi and *trans* Golgi. From the teachings of Tang et al. it would be obvious to those skilled in the art, that use of the Golgi retention signal in the chimeric polypeptide would direct said polypeptide to the Golgi or *trans* Golgi net work, where the polypeptide would undergo processing and be cleaved by a specific protease. One of ordinary skill in the art would have

been motivated to do so in order to detect, identify and or purify specific Golgi proteases that cleaves the polypeptide during processing in Golgi. One of ordinary skill in the art would have a reasonable expectation of success since Munro et al. teach the existence of proteases in the Golgi, Tang et al. provide sequences from glycosyltransferase known to direct a polypeptide to Golgi which could be used in the construction of a chimera, and Komoriya et al. provide the use of cleavage sites in such chimera and methods to detect protease activity. The construction of the above polynucleotide sequence into a vector such that the transcription of the chimeric polypeptide is controlled by a promoter, the use of such a vector to transform a host cell as well as to provide all the above in the form of a kit would all be well within the level of common knowledge of those skilled in the art.

Therefore the above invention would have been *prima facie* obvious to those skilled in the art.

In response to the previous Office action, applicants have traversed the above rejection at length. In summary, applicants argue that none of the cited references acknowledges or makes reference *to the need or desire of persons in the art to non-invasively assay proteases that are confined to the Golgi or ER* and that none of the references allude to the need or desire of persons in the art to identify compounds that can permeate the cell, enter the Golgi or ER compartment, and act on Golgi- or ER-resident proteases and therefore, a person of ordinary skill in the art, in view of the cited references, would have seen no need to target and confine a detectable protease substrate to the Golgi or ER. Applicants continue that, by logical extension, a person of ordinary skill in the art would have had no motivation to combine a Golgi or ER retention signal with a protease cleavage site and a reporter molecule.

Examiner respectfully disagrees with such a line of argument. Applicants are arguing a limitation that is non-existent in the claims. Claims are simply drawn to a chimeric polynucleotide comprising the various domains all linked together. Therefore, arguing that none of the cited references acknowledges or makes reference to the need or desire of persons in the art to non-invasively assay proteases that are confined to the Golgi or ER and that none of the references allude to the need or desire of persons in the art to identify compounds that can permeate the cell, enter the Golgi or ER compartment, and act on Golgi- or ER-resident proteases is highly misplaced. Furthermore contrary to such argument, Examiner would like to drawn the attention of the applicant to the teachings of Munro et al. according to which Golgi apparatus includes a huge diversity of enzymes such as those needed for glycosylation, for lipid synthesis as well as various proteases which specifically cleave specific proteins during processing. The reference also teaches that a second class of Golgi membrane proteins for which a localization determinant has been identified includes the proteases of the *trans* Golgi network. Thus the reference specifically teaches that proteins undergo not only glycosylation or palmitoylation etc. but also proteolytic processing during their passage through Golgi and that Golgi indeed has several types of proteases in house. Such teachings would indeed definitely motivate those skilled in the art to detect, identify or purify specific Golgi proteases. All that applicants have done is put together domains of specific polypeptides to identify a specific protease and such construction of chimeric sequences to identify specific proteases is well known in the art. Applicants argument that the references do not even acknowledge or make reference to the need for non-invasively assay proteases is highly flawed. Applicants are improperly reading the specification into the claims. While Examiner is required to analyze the

claims in light of the specification he is not required to use the teachings of the specification as claim limitations. Therefore, applicants whole argument is highly misplaced. Examiner acknowledges applicants' various arguments against each of the reference. However, none of those arguments are persuasive to overcome the above rejection. Hence the above rejection is maintained.

Claims 76-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sean Munro et al., Komoriya et al., and Tang et al. as applied to claims 65-66, 68-71, 73, 75, 81-96 above, and further in view of Steiner et al. (FEBS Lett. 463(1999):245-249) and Tomita et al. (J. Biol. Chem., 1998, Vol. 273(11):6277-6284. Claims 76-80 are specifically drawn to a composition comprising a polynucleotide encoding a chimeric polypeptide comprising a Golgi retention signal followed by a secretase cleavage signal such as β-secretase or a gamma-secretase cleavage signal comprising SEQ ID NO:3 or 4, followed by a reporter sequence such as a phosphatase enzyme or a fluorophore.

Steiner et al. teach the construction of a chimeric polynucleotide encoding a fusion protein comprising a recognition site comprising the protease cleavage sequence such as that of a secretase, γ –secretase, which is in turn linked to a reporter molecule such as a fluorophore and provide an assay for the identification of target proteases which cleave membrane-associated substrates and wherein the chimeric nucleic acid is operably linked to a promoter such as constitutive or inducible promoter, and wherein the chimeric nucleic acid is in an expression vector, expression cassette used to transform a host cell such as a Yeast cell. The reference, while discussing the different proteases involved in the formation of β-amyloid in Alzheimer's

disease teaches that such assays are useful in identification of compounds that inhibit such proteases. The reference also teaches that the purification of these enzymes (amyloid proteases) has been very difficult and therefore the chimeric polypeptides are useful in assaying the activity of these enzymes. While the reference teaches the development and use of membrane bound chimeric polypeptides for assay of the secretase enzymes, it is silent on the use of Golgi-retention or *trans* Golgi (ER) retention sequences as part of the chimeric polypeptide.

Tomita et al. teach more details of the processing of the amyloid polypeptide. The reference actually teaches without utilizing metabolic agents which non-specifically interfere with protein degradation and secretion, that amyloid precursor protein (APP) is cleaved after, or possibly during maturation (*O*-glycosylation) and that the cleavage occurs in compartments subsequent to *trans*-Golgi of the protein secretory pathway or possibly during the transport of APP through Golgi complex (see page 6277) and that such events may also be neuron specific.

With the teachings of the above two references in hand it would have been obvious to those skilled in the art that it would be more important to target the chimeric polypeptides such as those taught by Steiner et al. specifically to the Golgi apparatus by plugging in the Golgi retention signal such that the cleavage of such chimeric polypeptide can be monitored during its passage through Golgi and thereby identify the specific protease during the passage. In order to do that it would have been obvious to those skilled in the art to replace the GAL4 sequence (a yeast transcription initiator) in the chimeric polypeptide taught by Steiner et al. with a Golgi retention signal such as that taught by Tang et al. and use the protease cleavage sequence of either β-secretase or gamma-secretase and monitor the cleavage during the course through Golgi in order to study the fine molecular mechanisms involved in β-amyloid formation or monitor the

same in different neurons to identify which protease is involved in which type of neuron. One of ordinary skill in the art would have been motivated to replace the GAL4 sequence in the chimeric polypeptide of Steiner et al. as Tomita et al. teach that the APP is cleaved by α-, β-, and gamma-secretases in steps(s) during the transport of APP through Golgi complex. One of ordinary skill in the art would have a reasonable expectation of success since Steiner et al. and Komoriya et al. already teach the construction and use of chimeric polypeptides to detect proteases as well as demonstrate a working product or composition and Tang et al. provide Golgi retention signal sequences that can be used in making Golgi targeted chimeric polypeptides.

Therefore the above invention would have been *prima facie* obvious to those skilled in the art.

In response to the above rejection applicants have again traversed the rejection based on the same arguments as that used for the previous rejection. However, as pointed in the previous rejection, applicants base their argument by improper reading of the specification as claim limitation. Therefore, applicants' arguments are not persuasive to overcome the above rejection. Hence the above rejection is maintained.

Conclusion

None of the claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Manjunath N. Rao, Ph.D.
Primary Examiner
Art Unit 1652

September 20, 2005